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Original Article

Safety of inhaled (Tobi®) and intravenous tobramycin in young children with cystic fibrosis

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Abstract

Background: Use of inhaled tobramycin therapy for treatment of *Pseudomonas aeruginosa* infections in young children with cystic fibrosis (CF) is increasing. Safety data for pre-school children are sparse.
Methods: The aim of this study was to assess the safety of tobramycin solution for inhalation (TOBI®-TSI) administered twice daily for 2 months/course concurrently to intravenous (IV) tobramycin during *P. aeruginosa* eradication therapy in children (0–5 years). Audiological assessment and estimation of glomerular filtration rate (GFR) was measured prior to any exposure and end of the study.
Results: Data were available from 142 patients who were either never exposed to aminoglycosides (n = 39), exposed to IV aminoglycosides only (n = 36) or exposed to IV + TSI (n = 67). Median exposure to TSI was 113 days [59, 119]. Comparison of effects on audiometry results and GFR, showed no detectable difference between the groups.
Conclusions: Use of TSI and IV tobramycin in pre-school children with CF was not associated with detectable renal toxicity or ototoxicity.

Keywords: Aminoglycoside; Tobramycin solution for inhalation; Paediatrics; Cystic fibrosis; Adverse events

1. Background

Inhaled tobramycin has been a mainstay of treatment for those with cystic fibrosis (CF) for many years due to the excellent activity against *Pseudomonas aeruginosa* (*P. aeruginosa*) [1], the most common airway pathogen in CF. Tobramycin remains active after aeroionisation and is poorly absorbed across epithelial surfaces, thus achieving high concentrations in bronchial secretions with minimal systemic absorption [2]. Serum tobramycin concentrations after inhaled tobramycin are generally very low, with serum to sputum ratios of approximately 1% [3]. As a result, inhalation of tobramycin is anticipated to be associated with minimal systemic toxicity [4] in comparison to intravenous (IV) therapy which is known to be associated with increased risk of nephrotoxicity and ototoxicity [5–7].

Well recognised adverse events (AE) associated with aminoglycosides, and particularly tobramycin, include otovestibular and renal toxicity. Although precise mechanisms are unclear,

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it is likely that aminoglycoside-induced alteration of hair cell membrane permeability is integral to the ototoxic effects [7]. Similarly, nephrotoxicity is believed to occur as a result of retention of a portion of the administered dose in the cells of the proximal tubules of the nephrons [6]. Progression to renal failure is rare and recovery occurs upon discontinuation in most cases [8].

Treatment with tobramycin solution for inhalation (TSI), aimed at eradication of early *P. aeruginosa* infections is standard care in North America and frequently used in Europe and Australasia. There are few studies assessing the safety of TSI in young children. One small study using 300 mg TSI inhaled twice daily in 8 preschool children reported no AEs (changes in serum creatinine, audiometry and bronchospasm were assessed)[9]. A recent study including children aged 1–12 reported no AEs due to TSI although age of first exposure to TSI and methods for monitoring AEs were unclear [10]. Several studies have investigated inhaled tobramycin in older children and adults and reported very few treatment-related AEs. [1,11–13] The present study takes advantage of data from the Australasian Cystic Fibrosis Bronchoalveolar Lavage (ACFBAL) study which used TSI as part of the *P. aeruginosa* eradication protocol in preschool children [14]. Dosage and AE monitoring for IV tobramycin and TSI were protocol-driven over the entire 5 year study period, which allowed investigation of the safety profile of this medication.

2. Methods

2.1. Study and patients

The study design, protocol and other outcomes for ACFBAL study have previously been reported [14]. Briefly, the study which ended in December 2009, enrolled 170 infants diagnosed with CF across 8 sites in Australia and New Zealand and followed up until age 5 years.

Antibiotic treatment for *P. aeruginosa* infection included two weeks of IV therapy (once daily tobramycin commencing at a dose of 10 mg/kg, together with either 100 mg/kg ticarcillin–clavulanate three times a day or, 50 mg/kg ceftazidime three times a day). Tobramycin doses were adjusted by measuring 2 h and 6–14 h post-dose tobramycin concentrations and applying a linear regression method [15] aiming for an area under the concentration-time-curve of 100 mg/L.hr (with an acceptable AUC of 90 to 110 mg/L.h). Upon cessation of IV antibiotics, children received 56 days of TSI 300 mg (TOBI®) twice daily via a Pari LC Plus jet nebuliser with mask over a minimum of 15 min, or until nebulisation was complete. Concurrent oral ciprofloxacin (15 mg/kg twice daily) was administered for the first 28 days. As well as being used to treat proven infections with *P. aeruginosa*, IV antibiotics (including tobramycin) were administered to children who did not respond to outpatient treatment for a pulmonary exacerbation where *P. aeruginosa* was not detected upon microbiological culture. In these cases, the children did not receive follow-up treatment with TSI after completion of IV antibiotics.

For the present study all patients enrolled into the ACFBAL study with data available prior to any aminoglycoside exposure were included in order to compare the safety and toxicity between 3 distinct groups. The first group was designated 'never exposed' and children assigned to this group received neither IV aminoglycosides nor TSI during the 5 years. The second group; the 'IV only' group included children who received IV aminoglycosides treatment, predominantly tobramycin, but no TSI in the 5 years. Lastly, the third group, called the 'IV and TSI' group, as children assigned to this group received both IV aminoglycosides and inhaled TSI.

2.2. Safety assessment

Data collection included serum tobramycin concentration one hour after administration of TSI; renal function monitoring via estimation of glomerular filtration rate (GFR) and measurement of serum creatinine; audiometric function prior to and following exposure; and reported AEs. All comparisons were done between the first ever record and the closest to end of the study, unless specified otherwise.

2.2.1. Serum tobramycin concentration

The first dose of TSI was generally administered 24 h after cessation of IV tobramycin and normally after this first TSI dose tobramycin concentrations were measured 60 min. after the start of inhalation. Blood samples for tobramycin assay were collected via venipuncture or finger-prick depending on local practice. Investigations in April 2004 [16], demonstrated evidence for skin contamination with tobramycin after inhaled therapy affecting serum levels detected by finger prick. Consequently, samples taken via finger prick collections were analysed separately. The reported lower limit of quantification (LOQ) of tobramycin was 0.2 mg/L and thus any concentrations reported below LOQ were set to a value of LOQ/2.

2.2.2. Renal function

Cumulative renal toxicity over the study duration was assessed by comparing creatinine clearance at baseline (prior to aminoglycosides exposure) and creatinine clearance at the last measurement closest to end of study. These were summarised for each aminoglycoside group and mean differences compared. Creatinine clearance was assessed by estimating GFR using the Schwartz equation for pediatric patients[17].

To monitor the impact of an IV tobramycin course prior to TSI treatment on renal function, changes in serum creatinine concentrations measured within a patient during the same IV course were compared.

2.2.3. Audiometric function

Due to the age of the children in the study, the appropriate testing modality used at each audiometric assessment throughout the study was determined by the administering pediatric audiologists at each centre. Children were scheduled for screening audiometric assessments at baseline (<6 months of age prior to aminoglycoside exposure) and at 5 years at study completion. Those receiving inhaled TSI were scheduled for audiometry after

each exposure. Audiometry consisted of age-appropriate behavioural assessment including Visual Reinforcement Orientation Audiometry (VROA), Play Audiometry and Pure Tone Audiometry (PTA) to establish hearing thresholds and nature of any hearing loss present (conductive or sensorineural). Baseline testing may have included Auditory Brainstem Response (ABR) to assess neural function and predict hearing levels in infants in lieu of behavioural results. The ABRs were performed using a 'feed and wrap' natural sleep protocol in all but 6 infants, who had ABRs collected under general anaesthesia as they were performed on the same day as the baseline BAL Tympanometry was obtained where possible to assess middle ear function. Otoacoustic emissions (OAE) were performed in some centres involved in the study but not all, and are not reported formally.

2.3. Statistical analysis

Weight and height z scores were calculated from the 2000 CDC Growth Reference Charts (http://www.cdc.gov/growthcharts). Means and standard deviations (SDs) are presented for normally distributed data with medians and inter quartile ranges (IQRs) presented for skewed data. The change in GRF was analysed using a paired *t*-test while group comparisons of this change were made using linear regression. Corresponding 95% confidence intervals (CIs) for mean differences are shown. Non-parametric methods were used to analyse skewed data: Wilcoxon signed-rank test for paired data and Kruskal–Wallis when comparing groups. Analysis was performed using Stata V.12.1 (StataCorp, College Station, Texas).

3. Results

Of the 170 patients enrolled in the ACF BAL study, 26 patients received inhaled tobramycin or gentamicin instead of TSI and two patients did not meet the eligibility criteria, consequently 142 children contributed data to this analysis. There were 39 (27.5%) children in the 'never exposed' to aminoglycosides group, 36 (25.3%) children in the 'IV only' group (of which 61% received tobramycin only, 3% tobramycin and netilmicin, 8% tobramycin and gentamicin, 25% gentamicin only and 3% gentamicin and netilmicin), and the remaining 67 (47.2%) children comprised the group designated 'IV and TSI' were exposed to IV aminoglycosides and TSI (75% only to IV tobramycin, 1% to IV gentamicin only and 24% to IV tobramycin and gentamicin). Children in the 'IV only' group represents patients with negative *P. aeruginosa* cultures who received IV anti-Pseudomonal therapy based on lack of response to prior therapy. Demographics were well matched at baseline (Table 1).

Table 1
Participants and exposure to IV tobramycin and TSI.

	'Never expose'	'IV only'	'IV + TSI'
Number of patients	39	36	67
% Male	64	50	42
Weight at enrollment, *z-score*	−0.61 [1.0] [a]	−0.84 [1.2] [a]	−0.79 [1.1] [a]
Height at enrollment, *z-score*	n = 38 −0.36 [1.2] [a]	n = 35 −0.62 [1.1] [a]	n = 62 −0.57 [1.3] [a]
Age at first exposure to IV aminoglycoside (months)	–	18 [6.8, 34] [b]	19 [7.1, 33[[b]
Age at first exposure to TSI (months)	–	–	28 [15] [a]
Days on IV aminoglycosides	0	13 [6.5, 19] [b]	31 [19, 55] [b]
Days on TSI	0	0	113 [59, 119] [b]

[a] Mean [SD].
[b] Median [interquartile range].

3.1. Serum tobramycin concentration

Children in the 'IV and TSI' group received approximately twice the median number of days of cumulative exposure to IV aminoglycosides compared with children in the 'IV only' group although the age of first exposure (Table 1) was similar. The dose of the first course of IV tobramycin administered was different in the groups, with a mean of 10.3 mg/kg in the 'IV only' group and 12.0 mg/kg in the 'IV and TSI' group. This difference was present over the whole study period; the mean dose administered being 10.5 mg/kg and 12.1 mg/kg IV tobramycin, respectively. The median number of days on IV tobramycin for one IV course was 8 days in the 'IV only' group and 13 days in the 'IV and TSI' group.

Children in the 'IV and TSI' group received between 1 and 5 ([1,2], n = 67) courses of TSI. A course of TSI was defined as 2 months of TSI treatment as part of an eradication treatment. The median [interquartile range] number of days that patients received TSI during one course was 58 days [57,60]. In total, 52% of the samples taken revealed serum tobramycin concentrations below 1 mg/l, with 21% of samples being below LOQ. The median [interquartile range] concentration obtained from blood collected via finger prick (1.5 mg/l [0.9,4.2], n = 39) was higher than that from samples taken via venepuncture (0.6 mg/l [0.1,1], n = 45). The tobramycin concentration measured via finger prick ranged from 0.1 mg/l to 8.6 mg/l and via venepuncture from 0.1 mg/l to 4 mg/l. As expected, the tobramycin concentrations measured 1 hour post inhalation of TSI showed low systemic absorption.

3.2. Serum creatinine and renal function (Table 2)

A total of 37 pairs of serum creatinine concentrations measured within an IV course (median time between measurements 4 days [IQR: 2, 9]) in 24 patients were available for comparison. The first and last median serum creatinine concentrations within an IV period were 30 μmol/L [IQR: 20, 35] and 20 μmol/L [IQR: 20, 33], respectively. There was no evidence of a difference between the first and last serum creatinine concentration within an IV period (median difference 0 μmol/L, [IQR −7, 1], p = 0.43).

There was a minor difference, of no clinical significance, in the median GFR at baseline across the three groups. There was no difference in median serum creatinine concentration at the end of the study across the groups (p = 0.42, Table 2). The mean increase in GFR from baseline to study completion was 31 [95% CI 22 to 40]; p < 0.001. However, when adjusting for the baseline value and looking across aminoglycoside

Table 2
Serum Creatinine, renal and audiometric functioning before exposure to tobramycin and at study completion.

	'Never exposed' N = 39	'IV only' N = 36	'IV and TSI' N = 67
Serum creatinine	n = 36	n = 27	n = 52
Age (months) at first available serum creatinine record, pre exposure	7.7 [1.1,14]	2.6 [0.99,12]	2.0 [1.1,6.6]
Serum creatinine (μmol/L) at first available record, pre exposure	20 [20,32]	20 [20,23]	20 [20,38]
Age (months) at assessment of serum creatinine at study completion	59 [57,60]	60 [59,61]	60 [59,61]
Serum creatinine (μmol/L) at study completion	33 [26,40]	34 [20,37]	36 [27,40]
Renal Function			
GFR (ml/min/1.73 m^2) at first available record, pre exposure	101 [84,136]	105 [93,127]	95 [59,110]
GFR (ml/min/1.73 m^2) at study completion	111 [98,153]	120 [99,193]	109 [96,147]
Auditory Function	n = 29	n = 25	n = 49
Age(months) at first available assessment of auditory function, pre exposure	7.8 [3.6, 12]	4.7 [2.6, 9.4]	5.6 [3.8, 10]
Number with conductive hearing loss at first available record, pre exposure	1	1	6
Age(months) at assessment of auditory function at study completion	60 [59, 61]	61 [60, 62]	61 [60, 62]
Number with conductive hearing impairment at study completion	1	1	5
Number with sensorineural hearing impairment at study completion	0	0	1

Values are shown as median with interquartile range in brackets.

groups, there was no evidence of a difference between the 'IV only' or 'IV and TSI' groups compared to the 'never exposed' group (mean difference in GFR increase was 8.8 [95% CI −12 to 30]; p = 0.41 and 5.4 [95% CI −13 to 24]; p = 0.57, respectively).

When age at baseline and the time between pre- and post-exposure were added to the model, no difference in outcome was found. Fig. 1 shows the changes in GFR from the first to the last available record for the never exposed group and from pre- to post-exposure for the exposed groups. Fig. 2 shows the effect of repeated exposure to TSI on the change in GFR from baseline to the end of study measurement. Cumulative TSI exposure in days was divided into three groups: 1 course of TSI, 2 courses of TSI and 3 or more courses of TSI. There was no evidence of a difference in the change in GFR with 2 courses or 3+ courses compared to a single course of TSI (mean difference in GFR increase 1.8 [95% CI −22 to 26]; p = 0.88 and 21 [95% CI −11 to 53]; p = 0.19, respectively).

3.3. Audiometric function

One child was excluded from audiometric analysis due to the presence of a congenital sensorineural hearing loss in both ears. Another child was unable to complete the audiometry assessments due to co-existent autism. Further 37 of the remaining 140 children did not complete both pre and post audiometric testing, withdrew from the study, or were exposed to TSI or IV aminoglycosides prior to their first audiometric exam. Results for all remaining children are listed in Table 2.

Table 2 shows that the number of patients with normal hearing at baseline and the study end were 28, 24 and 43 in the 'never exposed', the 'IV only' and the 'IV and TSI' group, respectively. Conductive hearing loss or sensorineural hearing impairment between baseline and at the end of the study was found in 3.4%, 4.0%, and 12% of patients in the 'never exposed', the 'IV only' and the 'IV and TSI' group, respectively. One child in the 'IV and TSI' group was found to have a mild right-sided sensorineural hearing loss at study end and Fig. 3 shows the audiogram for this child. This loss could be attributed to ototoxic effects, as baseline

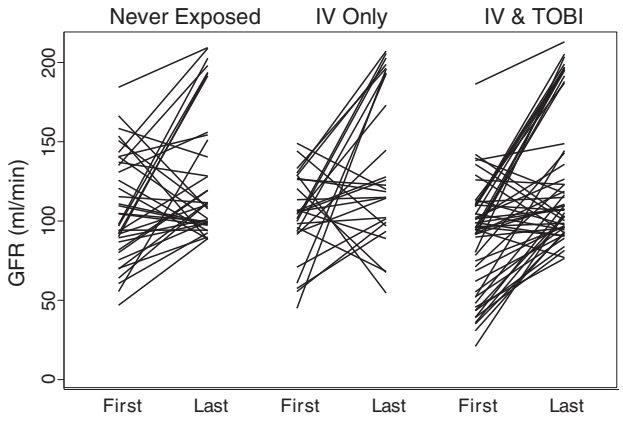

Fig. 1. Change in GFR (ml/min) from prior to aminoglycoside exposure (first) to study completion (last).

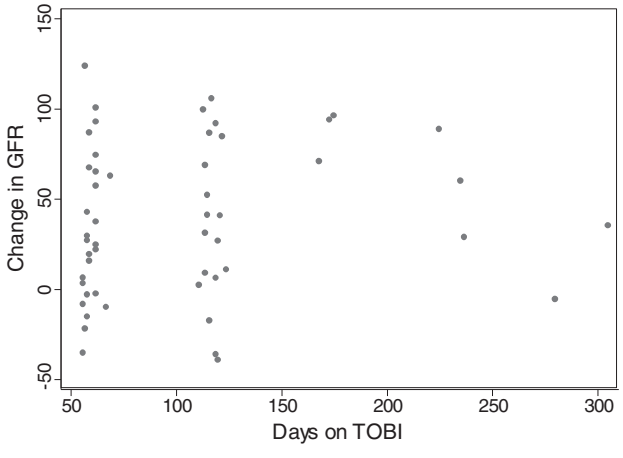

Fig. 2. Difference in GFR (glomerular filtration rate) for children exposed to inhaled tobramycin (TOBI®) by duration of the inhaled tobramycin course.

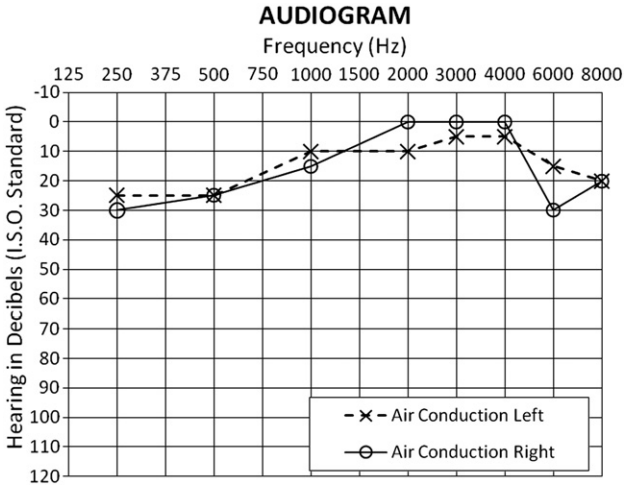

Fig. 3. Audiogram of child 710 exhibiting a mild hearing loss in the right ear.

audiometry showed no hearing loss present. This child inadvertently received a 300 mg (21.3 mg/kg) IV tobramycin dose instead of the nebulised TSI additionally to the usual IV tobramycin prescribed during the hospital admission, which was reported as a serious AE at the time.

3.4. Other adverse events

The most common AE in children exposed to TSI was voice alteration ('husky', 'hoarse' or 'lost' voice); reported on one occasion by 6 children. Other AEs assessed as having a causal relationship with TSI included: conjunctivitis (n = 2), tinnitus (n = 1), epistaxis (n = 1), rash (3 episodes in 2 children, n = 1 in the face and on trunk, n = 1 unknown location) and acute respiratory distress (n = 1). The acute respiratory distress resulted in cessation of TSI. Further, TSI was withheld from one of the children with rash until it resolved, but upon reinstitution of TSI the rash recurred and considered due to TSI which was discontinued permanently.

4. Discussion

In this study, we were able to prospectively examine every exposure to IV tobramycin and TIS in children from birth until 5 years of age. We found little evidence for drug-associated toxicity resulting from the use of IV tobramycin and TSI in young children with CF.

To achieve best efficacy high peak tobramycin concentrations are required [18], however high and cumulative exposure to aminoglycosides are linked to ototoxicity [5] and high trough levels are considered to influence the development of renal toxicity. In this study, the dosage of tobramycin administered intravenously was adjusted to achieve an AUC in a predetermined range. In addition, we adopted a once daily dosing regimen that is considered at least equally as safe, as multiple daily dosing [19]. This management may have contributed, at least in part, to the absence of any measureable renal or ototoxic effects in those exposed to IV tobramycin compared with those who were not.

It was found that higher doses and longer duration of IV tobramycin were administered to those in the 'IV and TSI' group, which was likely due to more targeted therapy in this group to eradicate *P. aeruginosa* and repeated drug monitoring leading to dose increases over time. Nonetheless, there was no difference in tobramycin specific AEs in this group.

While high serum tobramycin concentrations after inhalation of TSI were detected; mean concentrations were similar to those previously reported [20,21]. In general, peak serum tobramycin concentrations are reported to average <1 mg/L after TSI [1,12] with the highest concentrations being rarely above 4 mg/L [20,22]. While we are confident that the small numbers of very high levels we measured were the result of contamination with deposited TSI at the site of blood collection as reported previously [16,23] we cannot eliminate the possibility that there was a higher systemic exposure after administration of TSI in these children. Higher systemic exposures to TSI have been reported in those with well-preserved lung function [4] and this may be relevant for our study patient population.

Nephrotoxicity from inhaled aminoglycosides is rarely reportedly in children [24] and we found no evidence of nephrotoxicity in preschool children treated with TSI, some of whom had repeated courses of the drug. Limitations of using creatinine concentration as a marker for renal function are well known, as it is highly dependent on muscle mass, which changes as children grow. In addition, it is dependent upon diet, concomitant drug administration and hepatic function, which are all relevant in children with CF. The updated Schwartz formula used here to estimate GFR [17] may not be the most sensitive method for determining early renal dysfunction however each child served as their own baseline thus minimizing variations in GFR. GFR did, as expected, increase with age however at the end of the study there was no difference between the groups, providing reassurance for no detectable nephrotoxicity with exposure to IV tobramycin and TSI. We also found no relationship between cumulative exposure to TSI and tracking of GFR, mirroring and extending the previous report of Pedersen et al. for IV tobramycin exposure [25]. Ideally, more sensitive and predictive means of monitoring early renal impairment could be used in the future.

Studies of ototoxicity have conventionally used audiometric methodologies that require co-operation from the individual being assessed and this was an issue for our children prior to exposure as they were infants. Despite these difficulties we did employ effort-independent methods of audiometry to obtain baseline assessments of nerve and cochlear functioning and all testing was done by paediatric audiologists. We found one child with congenital hearing loss who was excluded from analysis as any deterioration in hearing thresholds could be attributed to congenital rather than ototoxic effects.

One child in the 'IV and TSI' group was found to have a mild right-sided sensorineural hearing loss at study end which was not noted at baseline assessment. The same child inadvertently received 300 mg tobramycin as IV instead of TSI, which highlights the importance of drug administration errors which can occur when different delivery methods of the same drug are used. All other children exhibited either normal hearing, or conductive

hearing loss at study end, suggesting that ototoxic effects related to tobramycin use are not largely evident in this young cohort. Few studies exist within this age range. Thomsen et al. reported no significant ototoxic effects of repeated courses of IV tobramycin administered over 2 week periods in young Danish children with CF with only one child exhibiting a transient high tone hearing loss [26]. Similarly, in spite of serum tobramycin concentrations up to 9.9 mg/l after inhalation of an intravenous form of tobramycin, Mukhopadhyay et al. were unable to find any significant abnormalities in their study of serial evoked response audiometry in children with CF [27].

Studies investigating ototoxic effects of tobramycin in older children and adults with CF suggest that a cumulative effect or genetic component may be involved [28,29]. Interestingly, there does not appear to be a correlation between aminoglycoside dose, peak serum levels, or number of courses, and level of hearing loss in CF patients [30]. Others suggest that the CF condition itself may actually provide a level of protection against the effects of aminoglycoside-based ototoxicity [30].

Some treatment-related AEs were found. Voice alteration was the most common adverse event in this group of 0–5 year olds. This was consistent with the known adverse event profile of TSI and previous reports in those with CF aged 6 years and older and those in the EPIC and ELITE studies [1,11,12] where the most common side effects were cough and dysphonia, also common to other inhaled therapies.

Thus, we conclude that although young children receiving IV aminoglycosides should have regular monitoring of renal function and preferably receive the first dose of TSI under supervision to monitor for immediate adverse effects. The data does not support the requirement for audiometric monitoring on a routine basis for either IV or inhaled exposure and no data to support routine monitoring of renal function with TSI as these drugs have an acceptable safety profile in preschool children with CF.

Conflict of interest disclosures

None to declare by Hennig, McKay, Cheney, Stacey, Vidmar, and O'Brien.

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Author contributions

SH, KMK, JC, SS, SV, KOB and CW contributed to the conception and design of the study, or acquisition of the data, or analysis and interpretation of data, drafting of the manuscript or revising it critically for important intellectual content. All authors approved of the final manuscript version to be submitted.

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Appendix A

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